In The United States Patent and Trademark Office

Appn. No.:	09/928,911
Appn. Filed:	08/13/2001
Applicant:	Mark Zamoyski
Title:	Compositions and Methods for Treating Lung Cancers
Examiner:	Rebecca Cook
GAU:	1614

Response to Office Action mailed June 22, 2004

Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Response to adverse affects of mycotoxins (page 3):

In response to page 3, paragraph 1, first two lines, regarding Hintikka's report that high concentrations of S. Atra spores caused severe inflammation in the lungs (page 69, col. 1) -- Hintikka states that spores without satratoxin caused inflammation, albeit milder, clearly indicating the spores were the cause of the inflammation and not the satratoxin. Acute inhalation exposure to trichothecenes alone, even in doses high enough to cause extensive systemic toxicity, "caused no changes in the upper respiratory tract or in lung tissue" (last paragraph of page 68 to first paragraph of page 69 of Hintikka's report). This is consistent with the disclosures in the specifications related both to the cell cycle active cytotoxic affects of trichothecenes (as lungs do not contain actively cycling cells) as well as the inability of trichothecenes to be recognized by the major histocompatibility complexes of the immune system because of both the inability to form peptide bonds (no nitrogen or amino acid structures) and because of their extremely small size (~ the size of a single amino acid). The application uses only purified trichothecenes, and in extremely low doses as provided in the specifications, in order to both avoid lung tissue damage and to avoid systemic toxicity issues (i.e. ng/ml doses are sufficient vs mg/ml used in most toxicity studies).

In response to page 3, paragraph 1, line 2 - 3, "that inhalation exposure to mycotoxins can either elevate cancer risk or cause kidney damage (abstract)" -- The relevant statement in Hintikka's abstract about mycotoxins is that "There is evidence that inhalation exposure to aflatoxins can elevate cancer risk, and inhalation exposure to ochratoxins can cause kidney damage". Although trichothecenes are fungal mycotoxins, not all fungal mycotoxins are trichothecenes. Aflatoxins, ochratoxins, and trichothecenes are completely different molecules as described in Hintikka's report on page 66, col. 2. Aflatoxins are produced by molds such as Aspergillus flavus oryzae that grows on peanuts and grain and aflatoxins are known carcinogens as enzymes that normally convert ingested toxins into harmless compounds (cytochrome P-450 oxidases) convert the aflatoxins into direct carcinogens (Molecular Biology of the Cell, Third Edition, Garland Publishing, 1994, page 1259). This is in stark contrast with trichothecenes which are converted into biologically inactive apotrichothecenes as disclosed on page 13 of the specifications. A World Health Organization report released in 1990 disclosed that ochratoxins have been shown in animal studies to accumulate in kidneys and could still be detected one month after

termination of exposure, however ochratoxins are also unrelated to present application. Compositions of present invention are trichothecenes, and the only statement Hintikka makes related to trichothecenes in the abstract is "In buildings with mould problems, trichothecene mycotoxins have been detected in building materials and dust samples. In these cases, residents have suffered from respiratory tract symptoms and irritation of eyes and skin". Inhalation of dust and mold, including spores and other airborne fungal particulates, plus a cocktail or various mycotoxins, could reasonably be expected to result in an allergic reactions in the respiratory tract or irritations of the eyes or skin, however this is not the same as selective inhalation of purified trichothecene that "caused no changes in the upper respiratory tract or in lung tissue" as mentioned above. The Hintikka statements on elevated cancer risk relate to aflatoxins and statements on kidney damage relate to ochratoxins, neither of which are used in present invention.

In response to page 3, paragraph 1, lines 4 - 6, "in epidemiological studies, mortality from all cancers and respiratory tract cancer was higher among workers exposed to airborne mycotoxins (page 67, column 2, paragraph 1)" -- The epidemiological studies on page 67, column 2 were for "workers exposed to airborne aflatoxins". As previously disclosed, aflatoxins are known carcinogens and are not used in present invention. Present invention uses trichothecenes, the molecular structures of which are disclosed in detail on pages 10 - 12 of the specifications.

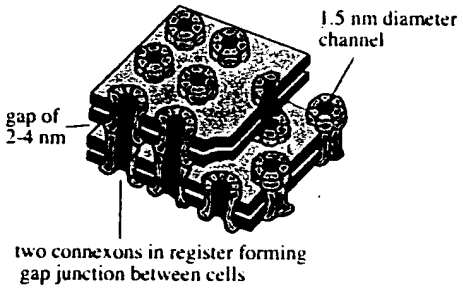
In response to page 3, paragraph 2 re: elevated cancer risk -- The present invention does not use aflatoxins, which is the compound that showed the elevated cancer risk. However, it should be noted that many anti cancer compounds in use today are both mutagenic and carcinogenic as they function by damaging DNA to achieve their cell cycle active cytotoxic affects. Alkylating agents are among the most widely used anti tumor agents and are efficient at cross-linking DNA, leading to strand breakage. Alkylating agents include cyclophosphamide, ifosfamide, melphalan, busulfan, mechlorethamine (nitrogen mustard), chlorambucil, thiotepa, carmustine, lomustine as well as platinum compounds such as cisplatin and carboplatin, which are not true alkylating agents also lead to covalent cross linking of DNA. The incidence of secondary leukemias from alkylating agents is about 2 percent and the incidence is augmented by the addition of radiation therapy, which is also carcinogenic. Accordingly, even if trichothecenes were ever proven to be carcinogenic, it would not preclude their use under prior art standards and furthermore because of the localization in the lungs as proposed under present invention, the other normal actively cycling cell populations, such as bone marrow, would be protected from any adverse or carcinogenic affects such as secondary leukemia.

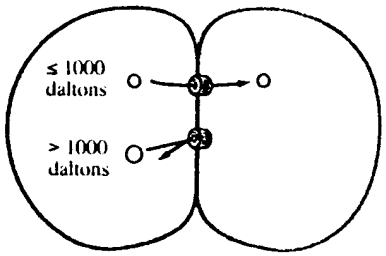
Response to Claims rejection under 35 USC § 103 (page 4):

In response to the claims rejection under 35 USC §103 on page 4 regarding unpatentability over 4,744,981 Pavanasasivam's conjugates of monoclonal antibodies with trichothecenes -- If "exposing" the body to trichothecenes for the purpose of "killing tumor cells" is the basis for unpatentability, then Pavanasasivam (4,744,981) would likewise not have been patentable over U.S. patents 4,332,732 and 4,352,936. The use of trichothecene as a chemotherapeutic by "exposing" the body to trichothecenes for the "purpose of killing tumor cells" dates back to U.S. patents 4,332,732 and 4,352,936 issued in 1982. Anguidine, a simple trichothecene, was administered in cytotoxic doses, however overall tumor

1982. Anguidine, a simple trichothecene, was administered in cytotoxic doses, however overall tumor response rate was low and there was considerable hematologic toxicity as disclosed on page 3 of the specifications. As a result, the use of trichothecenes was abandoned, and subsequent efforts and the related patents are focused on delivery methods to achieve tumor specificity and to avoid systemic toxicity. Applicant believes that both Pavanasasivam's approach of delivering the trichothecenes using monoclonal antibodies (4,744,981) and applicant's approach of reversal of direction of administration and using intercellular spacing and the gap junction transport system (6,342,520) are proper in that they both represent novel, unobvious, and useful delivery methods that could allow the use of trichothecenes against cancer and that the USPTO was correct in granting both patents.

Additionally, applicant's approach has significant advantages over Pavanasasivam's approach, the most notable of which is tumor penetration. Cells of a tumor stack up to 8 cells deep along a blood vessel. As disclosed on page 13 of the specifications, cells are spaced 2 - 4 nm apart and connexons in the bi-lipid cell membrane connect adjacent cells metabolically by what are referred to as gap junctions. Gap junctions allow molecules smaller than 1000 daltons or less than ~ 1.5 nm to pass. Amino acids range between .5 - 1 nm in size and as such individual amino acids are shared between cells but not macromolecules of amino acids.





Trichothecenes are extremely small at around 500 daltons ranging up to 750 daltons (or ~ .8 nm to ~1.2 nm). As such they are capable of dispersing via in the 2 - 4 nm spaces between cells and once internalized are capable of travel through the 1.5 nm gap junction transport system between cells. Pavanasasivam's conjugated trichothecenes are too large for traveling between cells or through gap junctions. Conjugating trichothecenes with monoclonal antibodies greatly increases their size. Adding a single average amino acid of ~ .7 nm to a 1 nm trichothecene already exceeds the 1.5 nm gap junction diameter preventing use of the gap junction transport system (and that is without provisions for linker molecules). A second amino acid already exceeds the lower limit of spacing between cells. Accordingly, Pavanasasivam's approach will not penetrate beyond the outermost cell layer whereas applicant's approach will completely penetrate the tumor. Furthermore, Pavanasasivam's approach is fraught with numerous other issues including 1) attaching an antibody to the trichothecene is no guarantee that the molecule will be internalized by the cell it is targeting, or 2) that the molecule will still retain its ability to bind to ribosomes and express its cytotoxic affects, or 3) that the conjugated trichothecene won't attach to other tissue types expressing similar cell surface markers and cause unacceptable systemic toxicity. Even if these issues are overcome, the conjugated trichothecene will still only penetrate the outermost cell layer of the tumor, making it highly unlikely that Pavanasasivam's approach will ever be reduced to practice.

Response to Claims rejection of Double Patenting (page 5):

In response to Examiner's objections related to double patenting related to applicant's patent 6,342,520 -- After careful review of the claims in patent 6,342,520, applicant agrees with examiner that the present claims may in fact be construed to be covered under patent 6,342,520. In particular, claim # 2 of patent 6,342,520 recites "or other means of delivering a drug interstitially into a tissue mass" and since examiner previously stated (on page 4 of the office action) that "inhalation therapy is well-known in the pulmonary art", it would follow that claim 2 of patent 6,342,520 would include inhalation. Accordingly, applicant respectfully requests to abandon the present application related to use of trichothecenes by inhalation against cancer in order to avoid a double patenting situation. Applicant would like to continue prosecution of divisional patent applications 10/696,863 for use of trichothecenes by inhalation against non malignant hyperproliferative conditions such as COPD and 10/694,236 for inhalable inhibitors of anaphylaxis in the lungs. Both of the divisional applications were generated as a result of Examiner's restriction requirement in an office action mailed on October 7, 2003.

Summary and Request for Abandonment:

In response to the office action mailed 6/22/04, applicant request the current application 09/928,911 be abandoned to avoid a double patenting issue.

Very respectfully,

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